Role and Importance of Vitamin D in Asthma and Other Allergic Diaseases

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ABSTRACT

Vitamin D is a steroid hormone that has important effects on bone metabolism and neuromuscular functions. Recent research has indicated that it also has a role in the development and treatment of allergic diseases by affecting the immune system through different mechanisms. After vitamin D is activated by liver and kidney in the body, it shows its effect by attaching to its receptor on the cell membrane. The vitamin D receptor is expressed on all tissue cells, particularly on those of the respiratory and intestinal epithelium by which extra-skeletal functions of vitamin D such as anti-inflammatory effects and immunomodulation are mediated. As a consequence, it is assumed that vitamin D and its receptor have effects on various systems in the human body. Some researchers suggest that deficiency or excess of vitamin D in the diet causes an increase in asthma and allergic diseases. Therefore, vitamin D supplementation is currently advised by some authors for the prevention and treatment of allergic diseases. It has commonly been reported that vitamin D is particularly found to be useful in preventing asthma attack and in managing resistant asthma. Currently, there has been an increase in the literature regarding the role of vitamin D in the treatment of atopic dermatitis and chronic urticaria-angioedema.

Keywords: Vitamin D, asthma, allergy, vitamin D receptor, eczema, urticaria

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INTRODUCTION

Asthma is an airway or chronic inflammatory obstructive disease in which genetic and environmental factors play a role, which is usually common in the lungs but variable and often reversible spontaneously or with treatment (1). In developed countries, there is a reported marked increase in the frequency of asthma and allergic diseases over the past past 2-3 decades. (2).

This increase is thought to be due to changing living conditions, such as changes in diet with vitamin D, trace elements, inadequate consumption of antioxidants, and varying rates of lipids, and environmental differences, such as hygiene and microflora change. The most common hypotheses in this regard are "diet," "hygiene," and "microflora" (3, 4).

The hygiene hypothesis, which tries to explain the incidence of allergic diseases, suggests that frequent infections in early childhood may convert the child's immune system into a non-allergic T helper 1 (Th1) pathway and reduce the risk of asthma and other allergic diseases (1). The microflora hypothesis that began to be more popular along with this hypothesis can help explain how the crowd in family (big family), birth order, and attending a day care center can reduce the risk of asthma and allergic disease (5–7). Recent increases in the predisposition toward the use of probiotics in the third trimester in a pregnant mother, in a baby after birth, and in various allergic diseases demonstrate the importance of hygiene and microflora hypotheses (3). Dietary vitamin D leads to allergic disease when it is in excess according to some, and when it is insufficient according to other studies (Figure 1).

In this review, we will discuss the positive effects of vitamin D on allergic diseases with various mechanisms, as in many diseases, in light of recent literature.

METABOLISM OF VITAMIN D

Vitamin D is a pro-hormone that is in steroidal structure and is required for the regulation of calcium (Ca) and phosphorus levels in blood, which are known to play important roles in bone metabolism and neuromuscular functions, and for the proper maintenance of bone regeneration cycle (8).

Vitamin D has two forms in humans. These are vitamin D2 (ergocalciferol, 25(OH)D2) and vitamin D3 (cholecalciferol, 25(OH) D3). Vitamin D3 is synthesized from 7-dehydrocholesterol in the skin with sunlight. 7-Dehydrocholesterol is first converted into pre-vitamin D3 with ultraviolet B sunlight by wavelengths ranging from 290 to 315. Then, vitamin D3 is derived from pre-vitamin D3 through isomerization. Vitamin D2 is formed as a result of the contact of plants with sunlight. Vitamin D3, which is formed by sunlight, fulfills 90%–95% of the amount that is needed by the human body. Vitamins D2 and D3, which are derived from foods

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and synthesized in the skin, are converted to 25-hydroxyvitamin D2 (25(OH)D2) and 25-hydroxyvitamin D3 (25(OH)D3) in the liver. As 25(OH)D is synthesized in the liver, it is transported to the kidney tissue by binding to the vitamin D-binding protein (DBP). The 25(OH)D vitamin released from the DBP-25(OH)D vitamin complex entering the renal tubules return to $1,25(OH)_2D$, which is the active form of vitamin D and 1-α-hydroxylase enzyme in the mitochondrial cytochrome P450 enzyme system (9).

Calcitriol (25(OH)D) is used to describe both 25(OH)D3 and 25(OH)D2 levels. Blood 25(OH)D level is the best indication of tissue vitamin status. For this reason, it is the basic parameter used to evaluate vitamin D deficiencies. The major form of vitamin D in the circulation is 25(OH)D3 with a half-life of approximately 2–3 weeks. Plasma $1,25(OH)_2D$ level may be normal or even higher in cases of deficiency; therefore, it is not used to evaluate the status of vitamin D (10–13). For serum 25(OH) D3 level, normal values are accepted as 30–100 ng/mL (75–250 nmol/l), insufficiency is 21–29 ng/mL (51–74 nmol/l), and deficiency is <20 ng/mL (<50 nmol/l) (3). Although these are the values required for vitamin D to be effective in calcemia/bone, these are the same levels sufficient to be effective on other systems, including extracalcemic (non-bone) tissues or immune system (Table 1), or are higher levels required? Further studies are needed in this regard (10–13).

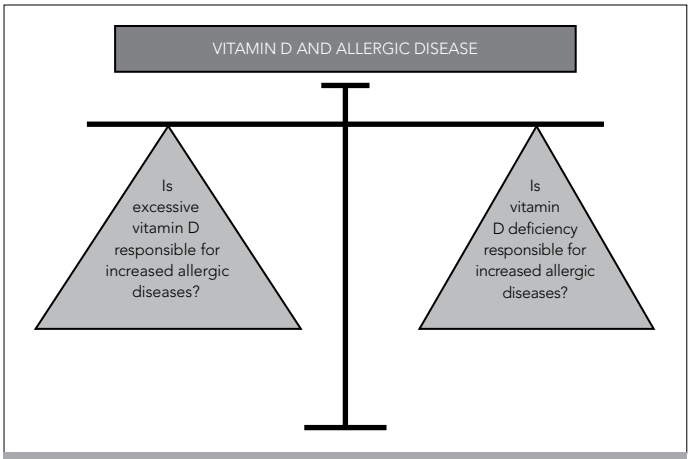

Figure 1. Two hypotheses showing the effect of vitamin D on allergic diseases are presented

The active $1,25(OH)_2D$ gains functionality with two pathways within the cell. These are the "genomic" and "non-genomic" pathways. The $1,25(OH)_2D$ that is transported to the tissues via DBPs in the genomic (through genes) pathway enters the cell and complexes with the vitamin D receptor (VDR). This complex binds to specific DNA regions as a ternary complex by taking the retinoic acid X-receptor together. While the resulting ternary complex causes some genes (osteocalcin, Ca-binding protein, and 24-hydroxylase) to be transcribed, it decreases the transcription of some genes (inflammatory genes, interleukin (IL)-2, and IL-12). In the non-genomic pathway, vitamin D activates secondary signaling pathways in the cytoplasm by binding to VDRs on the plasma membrane. This receptor is expressed in all tissues and is responsible for the extracellular function of vitamin D. As a result of this pathway, the Ca channels in the cell membrane are activated. The non-genomic pathway is rather active in the pancreas β cells, smooth muscles, heart muscles, intestinal cells, and monocytes. It has been suggested that this pathway is associated with the development of psoriasis, type I diabetes, rheumatoid arthritis, multiple sclerosis, Crohn's disease, hypertension, cardiovascular disease, and some common cancers (9, 14).

FUNCTIONS OF VITAMIN D IN THE BODY

Vitamin D increases Ca absorption in the kidneys, bones, and intestines. It takes effect in the distal tubule cells together with the parathyroid hormone (PTH). A total of 1% of Ca filtered from the distal tubules is absorbed. It acts on bone tissue and increases Ca mobilization. It acts together with PTH for this. Vitamin D that binds to the VDR in the intestinal epithelial cells increases the synthesis of Ca-binding protein, thereby increasing the active transport of Ca. In addition, in studies conducted on vitamin D in recent years, it has been known that it has an effect on many systems other than bone metabolism (8–14). The VDRs, which are expressed in all tissues, especially in the respiratory and intestinal epithelium, and which are responsible for the functions of non-skeletal vitamin D (anti-inflammatory and antiproliferative), are also receptors that are found in T or B lymphocytes and mononuclear cells and are responsible for immunomodulation (Figure 2).

VITAMIN D AND ITS IMPACT ON THE IMMUNE SYSTEM

The effect of vitamin D on natural immunity manifests itself with supporting antimicrobial functions and with suppressing inflammatory activity. The treatment of human monocytes with calcitriol

Table 1. Vitamin D levels and their meanings for human health

Vitamin D state	Ng/mL	Nmol/L	Its importance for health
Deficiency	<20	<50	Associated with rachitism in infants and children and osteomalacia in adults
Insufficiency	21-29	52.5-72.5	Generally accepted to be insufficient for bones and general health condition in healthy individuals
Sufficiency	≥30	>75	Generally accepted to be sufficient for bones and general health condition in healthy individuals
Extra-calcemic effect	≥30 (?)	>75 (?)	Immunomodulation
Toxicity	>100	>250	Potential emergent side effects at high levels

Conversion of units: 1 Ng /mL=2,496 Nmol /L

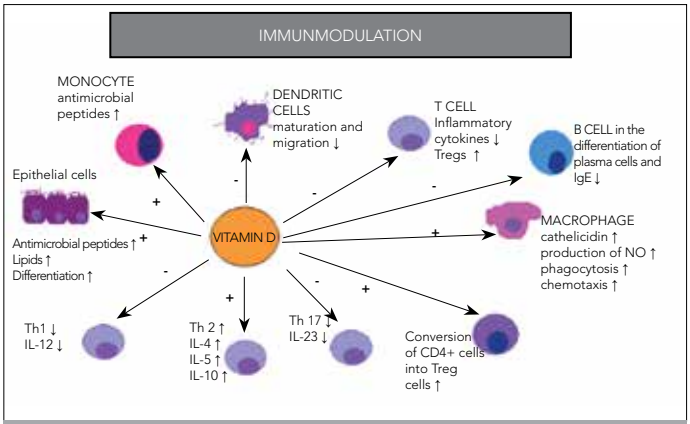

Figure 2. The effects of vitamin D causing modulation in innate and acquired immune system cells are shown

inhibits the expression of Toll-like receptor (TLR)-2 and TLR-4 from TLRs. TLR is important for the early onset of inflammatory immune response. Decreasing TLR expression in monocytes with calcitriol reduces the production of tumor necrosis factor-α, which is among the proinflammatory cytokines. In addition to the inhibition of the inflammatory functions of innate immune cells, vitamin D also decreases the acquired effective immune response and stimulates the synthesis of antimicrobial peptide (AMP), primarily cathelicidin. This explains the relationship between vitamin D deficiency and infections (15, 16).

In dendritic cells, the surface expression of antigen-presenting molecules (CD1a, major histocompatibility complex class II, and costimulatory molecules CD40, CD80, and CD86) diminishes in the presence of calcitriol and does not fully mature. Proinflammatory cytokine IL-12 production decreases, and anti-inflammatory cytokine IL-10 production increases (Figure 2). This effect is realized with the increase in the CD4+ Treg cell population that directly acts on CD4+ T cells and secretes IL-10 (17).

After $1,25(OH)_2D$ reaches the nuclear receptor and is activated, there is a decrease in the conversion of monocytes to macrophages, resulting in decreased antigen presentation of macrophages to T lymphocytes. In addition, both immunoglobulin synthesis from B lymphocytes and maturation of antigen-presenting dendritic cells are suppressed (Figure 2). Thus, sensitivity reactions that are delayed due to B cells are inhibited by $1,25(OH)_2D$. In addition to antiproliferative activity, it also inhibits the formation and functions of natural killer lymphocytes via the lymphocytes activated as a result of the activation of the VDR (18).

VDR POLYMORPHISM

VDR, which is a member of the nuclear receptor family and is expressed in all tissues, is responsible for extracellular vitamin D functions. The effect of VDR has been demonstrated on 291 genes and 80 different metabolic pathways. $1,25(OH)_2D3$ upregulates 2/3 of these genes (the expression increases) and downregulates 1/3 of them (the expression decreases) through VDR. Some of the non-bone effects on the respiratory and intestinal epithelial barrier are antioxidant, anti-inflammatory, antiproliferative, and immunomodulation effects (15–18).

Recently, the role of VDR polymorphisms in the development of asthma has begun to be revealed. For example, in addition to the fact that VDR knockout mice have been shown to be resistant to asthma, it has been shown that the induction of bronchial hyperreactivity and inflammation is inhibited in patients with hereditary vitamin D-resistant rickets that develops as a result of the mutated VDR (19). As a result, it has been shown that the development of asthma can be prevented as a result of VDR elimination or mutation. In addition, it has been shown that the control and recovery of the disease and daily activities can be easily provided in patients with asthma with ApaI a allele of the VDR rather than TaqI, BsmI, and FokI C alleles (20). It has been reported that this VDR polymorphism establishes a ground for the development of asthma in people with TaqI, BsmI, and FokI C alleles (21). This literature suggests that not only vitamin D but also its receptor (VDR) may be important in the development of asthma and allergic diseases.

CAUSES AND CONSEQUENCES OF VITAMIN D DEFICIENCY

The most frequent cause of vitamin D deficiency is the inability to get enough exposure to sunlight, wearing closed clothes, and lack of dietary intake (especially seafood). Vitamin D deficiency can also be seen in some cases, such as geographical location, sunscreen, depth of skin color, some medications (anticonvulsant, rifampin, glucocorticoids, and antiretroviral, among others), hepatic–renal insufficiencies, nephrotic syndrome, and diseases leading to obesity and malabsorption (Crohn's, celiac, and Whipple's diseases and cystic fibrosis, among others) (8-12).

The most common diseases that occur after the deficiency are rickets and bone diseases, such as osteomalacia and osteoporosis. In addition, it has been found to be associated with schizophrenia, depression, a tendency for infections, lung and cardiovascular diseases, and even with cancer tendency. Vitamin D also has an effect on autoimmune diseases (8–14). Its effects on allergic diseases, such as asthma, in the immune system will be explained further in this review.

VITAMIN D AND ITS RELATIONSHIP WITH ASTHMA BRONCHITIS

The effect of vitamin D on asthma development and treatment is summarized in Table 2 and will be further discussed here. There are several hypotheses regarding the effect of vitamin D on allergy development. First, the increase in allergic diseases is thought to occur because the excessive use of vitamin D makes the Th2 response dominant. Vitamin D supplementation in the maternal period (pregnancy) and early childhood was considered to be responsible for this (Figure 1). Second, the increase seen in allergic diseases, such as asthma, is related to the widespread lack of vitamin D, and there are studies suggesting that this is caused by vitamin D deficiency, which affects Treg cells (22–25).

Vitamin D Level in Pregnancy or Birth and Allergic Disease Development (Birth Cohorts)

In many large birth cohort studies, the relationship between vitamin D supplementation during infancy and the development of asthma and allergy in the later period was investigated (26). The results of these studies that evaluated the vitamin D level of the

mother during pregnancy and the risk of allergy development are conflicting and insufficient.

Studies have been conducted to prove that high level of maternal plasma vitamin D (25(OH)D3) in late pregnancy is associated with an increased risk of eczema (atopic dermatitis) in 9-month-old infants (27). However, in some other studies, recurrent wheezing was found to be less frequent in children of mothers, receiving higher amount of vitamin D during their pregnancy, when they reached 3 years old (28, 29). It has been shown in some studies through 25(OH)D levels in the cord serum that there is an inverse relationship between multitrigger wheezing at 2 years and the risk of wheezing development at 5 years (30, 31). However, it was found that the rate of wheezing is lower at 5 years old as a result of maternal vitamin D supplementation (32), but in another study, the use of 400 IU/day maternal vitamin D versus 2800 IU/day does not cause a significant decrease in this disease at 3 years (33). It was shown in the study conducted by von Mutius et al. (34) that prenatal vitamin D does not prevent the development of asthma in children. The Vitamin D Antenatal Asthma Reduction Trial study, which was a study to reduce asthma using vitamin D in the antenatal period, compared the effect of 4400 IU/day versus 400 IU/day vitamin D given to 806 risky pregnant mothers at the end of 3 years, and the incidence of asthma decreased by 6.1% in children born, but it was not found to be significant (35).

These results indicate that vitamin D may be important in the development of allergic disease when given in pregnancy or in early childhood. It is thought, however, that varying doses of vitamin D may alter the effect of the pathogenesis of allergic disease and asthma.

Asthma Prevalence and its Relationship with Serum Vitamin D Levels

In the study conducted in adults aged 21–50 years by Confino-Cohen et al. (36), 4-year hospital records were examined, and vitamin D measurements were made in 307,900 or 1,783,334 patients, and 21,737 (6.9%) of these were found to have doctor-diagnosed asthma. There was no relationship between doctor-diagnosed asthma prevalence and vitamin D levels. In a systematic compilation of cohort studies conducted by Rajabbik et al. (37), the relationship between low vitamin D levels and the diagnosis of asthma in children has not been clearly demonstrated.

Relationship of Vitamin D with Asthma and Respiratory Tract Infections

Vitamin D has been found to be effective on the predisposition and responsiveness to the infections triggering wheezing at early ages (38). It is thought that vitamin D reduces respiratory tract infections (respiratory syncytial virus and rhinovirus, among others) and consequently contributes to the prevention and control of asthma. It is also thought that vitamin D can prevent asthma attacks with different mechanisms. It accomplishes this with immunomodulating, as well as antimicrobial, effects by increasing the synthesis of AMP proteins, such as β-defensin and cathelicidin, and by reducing nuclear factor kappa β-related chemokine (CXCL10) and interferon-β secretion induced by the virus in the respiratory epithelium (39).

In the National Health and Nutrition Examination Survey III trial, patients with low 25(OH)D3 levels were found to have a higher upper respiratory tract infection rate, which is independent of the season and more prominent in patients with asthma (40). In some studies, it has also been shown that the use of vitamin D is beneficial during asthma attacks (41). In another study, >300 Japanese school children were examined, and a 4-month use of 1200 IU/day vitamin D showed that 42% of the children had less influenza A infection, and patients with asthma had six times fewer attacks (42). Childhood Asthma Management Program, a cohort study, was performed in 1024 children, and fewer severe symptoms and sequelae due to viral infections were observed (43). In a meta-analysis of five studies, it has been concluded that vitamin D supplementation (500 IU/day) in children may be beneficial in preventing attacks and controlling asthma (44). However, as there are also studies showing the opposite, there is still not enough data and consensus on this issue (45).

Effect of Vitamin D on Lung Functions

There are clinical observational studies showing that low vitamin D (25(OH)D3) levels are associated with impaired lung capacity (↓ forced expiratory volume in one second/forced vital capacity) and increased bronchial responsiveness. In addition, low vitamin D levels increase the risk of asthma exacerbation and steroid need and lead to steroid non-responsiveness, poor asthma control, and increased hospitalization (41–45). Higher vitamin D levels have also been found to be associated with better lung functions. In a cross-sectional study, the analysis of 25,000 adults showed a strong association between low serum 25(OH)D3 levels and decreased lung function (46). In another study, it was shown that low vitamin D levels at birth are associated with high airway resistance in childhood (47).

Treatment-Resistant and Steroid-Resistant Asthma

Vitamin D is thought to play an important role in asthma and allergic diseases due to its immunomodulatory properties (Figure 2) (48). In addition, the severity and poor control of the disease have been found to be associated with vitamin D levels in patients with vitamin D deficiency and inadequacy. There are also studies proving that steroid need is associated with disease severity or exacerbation and vitamin D levels (49). It is known that vitamin D has a modulatory effect on the smooth muscle of the respiratory tract and an effect reducing eosinophilic inflammation (50). It has also been shown that active vitamin D suppresses elevated levels of IL-17A in resistant asthma and reverses impaired induction of T regulatory cells (51). In addition to these data, it has been noted in other studies that patients with more severe asthma may have lower levels of vitamin D because of fewer outdoor activities and less sun exposure (23).

Studies Performed in Patients with Asthma and Reported from Turkey

In addition to the studies performed in steroid-resistant patients in our country, the relationship between childhood asthma and vitamin D deficiency was questioned in the study by Uysalol et al. (52), and an inverse relationship was observed between vitamin D deficiency and asthma. There are also studies reporting that asthma is associated with a high level of vitamin D deficiency and insufficiency, that the disease is more severe, and that there is an association between poorly controlled asthma and vitamin D levels (49).

Vitamin D and its Effects on Allergen Immunotherapy

It has been shown that the use of vitamin D during allergen immunotherapy increases the long-term effect of specific immunotherapy in allergic mouse models (53). Clinical and immunologic efficacy of immunotherapy in young patients with asthma was found to be correlated with 25(OH)D serum concentration. In a previous study, it was found that the effect of immunotherapy on reducing asthma symptoms and its effect freeing from the corticosteroids are more significant in those who had a high vitamin D level and underwent subcutaneous immunotherapy due to mite allergy (54). Combined use of vitamin D was shown to be more effective in reducing nasal and asthma symptoms in those who had allergic rhinitis and received sublingual immunotherapy specific to five different weed pollens (55).

VITAMIN D AND ITS RELATIONSHIP WITH OTHER ALLERGIC DISEASES

Vitamin D and its effect on the other allergic diseases are summarized in Table 2. It will be further detailed in light of recent literature as follows.

Vitamin D and its Effect on Allergic Rhinoconjunctivitis

Serum vitamin D levels in 49 patients with seasonal allergic conjunctivitis were found to be significantly lower than those in the control group in a study conducted in Konya, Turkey (56). In a study published in Norway in 2014, whereas low serum vitamin D levels in 1351 adult patients were found to be associated with increased risk of allergic rhinitis in men, they were associated with a reduced risk of allergic rhinitis in women. However, it has also been considered that this may be because female gender hormones can influence the immune response in the direction of Th1 (57). Although controversial results were obtained in studies reported in Korea, the serum levels of vitamin D were shown to be higher in patients with vasomotor rhinitis in the control group, and they were higher in those with allergic rhinitis (58). Similarly, in the studies reported from Turkey, low serum vitamin D levels were detected in patients with allergic and non-allergic rhinitis in comparison with the control group (59, 60). On the contrary, serum vitamin D levels were found to be higher in those with allergic rhinoconjunctivitis than in those in the control group (61).

Vitamin D and its Relationship with Atopic Dermatitis

In some studies, it was suggested that there is a negative relationship between vitamin D levels and the prevalence and/or severity of atopic dermatitis, and vitamin D deficiency was observed to be more prominent in patients with allergic sensitization and/or with severe disease (62). Observationally, it is known that the disease is common in the period when the sun is less. The use of heliotherapy (narrowband ultraviolet B) has also been demonstrated in anecdotal studies. Vitamin D is thought to be involved in the formation of the stratum corneum barrier and in the synthesis of proteins such as filaggrin, via the regulation of keratinocyte proliferation and differentiation. It is also thought to reduce microorganism colonization (63, 64). Consistent with this information, in many clinical trials, a reduction in high SCORing Atopic Dermatitis (SCORAD) score and clinical improvement was reported in patients with eczema as a result of the use of vitamin D (65). However, recent studies have also shown that vitamin D supplementation does not have an effect on eczema severity (66).

Vitamin D and its Effect on Food Allergy

Geographical location (exposure to sunlight) was found to have a directly proportional correlation with food allergy, and anaphylactic development was found to have a directly proportional correlation with adrenaline auto-injector usage. Similar findings have led to the development of the hypothesis of vitamin D–anaphylaxis (67). In countries such as Australia, the use of adrenaline auto-injector was found to be inversely correlated with melanoma development. Indirect exposure to sunshine has been shown to reduce the development of food allergy (68).

There are studies that indicate that vitamin D deficiency may cause food allergy allergy by causing impaired immunity balance, increased Th2 lymphocyte ratio, and decreased number of T regulatory and tolerogenic dendritic cells, in addition to abnormal bowel barrier permeability (69).

Vitamin D and its Effect on Chronic Urticaria and Angioedema

Thorp et al. (70) showed that adult patients with chronic urticaria were found to have lower levels of vitamin D than the control group. Vitamin D supplementation may be beneficial in these patients with the immunomodulatory effect. Goetz et al. (71) also found vitamin D treatment as successful at a rate of 70% in idiopathic urticaria and angioedema (72, 73).

Table 2. The role of vitamin D in asthma and other allergic diseases

Disease	Effect of vitamin D	Mechanism of action	References
Asthma bronchitis	↓↑	Th2↑↓, Th1↑, Treg cell ↑, AMP↑, β-defensin↑, cathelicidin ↑, CXCL10 in the respiratory epithelium and IFN- β↓	22-55
Allergic rhinitis	↓↑	Th2↑↓, Th1↑, Treg cell ↑	56-61
Allergic conjunctivitis	↓↑	Th2↑↓, Th1↑, Treg cell ↑	56-61
Atopic dermatitis (Eczema)	↓↑	Stratum corneum↑, filaggrin↑, keratinocyte ↑, microorganism colonization↓	62-66
Urticaria /Angioedema	↓	Immunomodulation	70-73
Food allergy	↓	Intestinal permeability ↓, Th2↓, Treg cell↑ , tolerogenic dendritic cell ↑	69

↓: decreases the severity of the disease, ↑: increases the severity of the disease, ↑↓: both increases and decreases the severity of the disease

CONCLUSION

Although the lack of vitamin D is suggested to be higher particularly in asthma and in other allergic diseases, its routine use in the prevention and treatment of allergic diseases is still not recommended (74). Serum 25(OH)D3 examination should be requested in dark-skinned patients with asthma (African-American and Hispanic-American), obese people, old people, those who work indoors and in an office, and those who live in places with less sunlight. In addition, there are recommendations to use vitamin D3 in moderate doses (1000–2000 IU/day) in asthma, especially in patients who use frequent systemic steroids and in patients with treatment-resistant asthma (75). It is also thought to be useful in patients with atopic dermatitis and chronic urticaria. The role of vitamin D in asthma and other allergic diseases is shown in Table 2.

Although we do not have an experience of using vitamin D in allergic diseases, as we interpreted in light of the recent literature, we have concluded that the use of vitamin D in selected patients with asthma may be beneficial. Therefore, there is a need for more studies for the determination of the proper dose, time, and person's genotype in order for vitamin D to be used routinely in allergic diseases, and these important data need to be clarified in the future.

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